found at laparotomy in Case III make it clear that perforation results from gangrene supervening on gross bruising, and that many patches of bruising do not lead to gangrene and perforation, so that too early laparotomy might defeat its purpose if perforation were to occur subsequently. However, the findings point to the necessity for exploration of the abdomen in cases of this type, and in future one would prefer to explore—even in the early hours—and find nothing more than bruising of the viscera, and would be prepared to operate a second time if a later perforation occurred.

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INTOLERANCE TO LIVER EXTRACT IN PERNICIOUS ANAEMIA

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It is a matter of common experience in clinics devoted to the treatment of pernicious anaemia that a certain small proportion of patients treated with liver by the parenteral route in course of time become "sensitive" to the injections. In such cases treatment may successfully be carried on by the oral route; this method of administration of liver extract is, however, extremely wasteful, and the Ministry of Health has made an Order, dated May 21, 1941, under Regulation 55 of the Defence (General) Regulations, 1939, which lays it down that liver extracts shall not be administered otherwise than by injection. At the suggestion of Dr. S. C. Dyke, Director of the Pathological Department of the Royal Hospital, an inquiry has therefore been undertaken into the possibility of inducing patients who had become sensitive to liver to tolerate their requirement by parenteral injection.

Out of about 200 patients with pernicious anaemia attending the department over the past fifteen years 14 were known to have become intolerant to liver by parenteral injection. None of these gave any previous history of allergic manifestations, but in all cases the symptoms of intolerance were those usually associated with allergic hypersensitivity. These ranged from slight local manifestations at the site of injections, such as redness, induration, and itching, through all gradations up to severe constitutional reactions associated with generalized urticaria, vomiting, failure of vision, and attacks of typical spasmodic asthma. In some cases the symptoms were alarming, and necessitated the detention of the subjects in hospital; in the milder cases they responded readily to ephedrine by mouth, and in the more severe to adrenaline hypodermically. It was found that once sensitization had been established it extended to all brands and types of liver extracts; attempts to carry on treatment with preparations other than those responsible for the sensitization were uniformly unsuccessful. In some cases the allergy was only transient; in others it was persistent and had necessitated a change-over to administration by the oral route. Three cases of this latter type formed the subject of this investigation.

Treatment of Three Cases

Case 1.—Man aged 52. Under treatment for pernicious anaemia since May, 1939. Maintenance dosage, 4 c.cm. of liver extract parenterally every six weeks. In Oct., 1940, after the usual injection he developed generalized urticaria, with puffiness of the face and failure of vision; thereafter he was treated with liver extract orally, 1 oz. daily, until Dec., 1941, when it was decided to attempt desensitization. Intradermal tests with 0.1 c.cm. of two different brands of liver extract gave strongly positive skin reactions. The attempt at desensitization was begun with a dose of 0.1 c.cm. of liver extract, which was tolerated well; increments of 0.1 c.cm. were made at each successive dose, given every second day until a

dose of 1 c.cm. was reached; thereafter an increment of 0.2 c.cm. was used. The patient attended every third day, and remained in hospital for two hours after each injection until he could tolerate 3 c.cm. of liver extract in one dose. This dose was increased by 0.5 c.cm. at two-weekly intervals until 4 c.cm. could be given in a single injection. The patient now tolerates this dose every four to five weeks, and on it a normal blood picture is maintained. On some occasions after this injection of 4 c.cm. of liver extract he complains of slight headache and shows some swelling of the forehead; this disappears on giving ephedrine. He is admitted to hospital for two hours for each monthly injection; probably it will be possible to dispense with this precaution in the future. The intradermal tests with liver extract are still strongly positive, though less so than before desensitization.

Case 2.—Woman aged 61. Under treatment for pernicious anaemia since May, 1939. On maintenance dose of 4 c.cm. of liver extract parenterally every two months until 1940. In March, 1940, she collapsed after her injection; the same thing happened again in May, 1940. Treated by liver extract orally, at first 1 oz. and later 2 oz. daily. This dose was not enough to maintain a normal blood picture, and in Sept., 1941, it was decided to attempt desensitization. Somewhat surprisingly, skin tests with liver extract gave negative results. For the next five months she was admitted to hospital for one day every four weeks and received her liver extract parenterally in divided doses, starting with 0.1 c.cm., with increments of 0.1 c.cm. every 20 minutes so long as no reaction occurred; on the occurrence of a reaction time was allowed for the symptoms to subside, when the previous dose was repeated. The reactions consisted of tachycardia, vomiting, and malaise; there were never any dermal manifestations. By Jan., 1942, the patient tolerated a dose of 2 c.cm. of liver extract in two injections of 1 c.cm. at an interval of one hour. At this time the state of the blood was not satisfactory, but an attempt to raise the total dose to 2.5 c.cm. resulted in severe collapse. In March, 1942, owing to the unsatisfactory state of the blood picture she was admitted to hospital. She then received 6 c.cm. of liver extract parenterally in divided doses over two days. After a single dose of 1 c.cm. she developed for the first time generalized urticaria, and intradermal tests with 0.1 c.cm. of liver extract were found to be strongly positive. In spite of this she now tolerated a dose of 0.5 c.cm. of liver extract, and a desensitizing course was started from this level with increments of 0.1 c.cm. daily up to a single dose of 1.5 c.cm. This injection, however, again gave rise to generalized urticaria, and had to be repeated the next day, when it was well tolerated. Desensitization was thereafter continued with increments of only 0.1 c.cm. up to a dose of 2 c.cm., and later of 0.5 c.cm. until 4 c.cm. was tolerated in one dose. A total of 34.5 c.cm. of liver extract was given in 21 days. The patient now receives 4 c.cm. of parenteral liver extract in a single dose every four weeks without disturbance.

Case 3.—Female aged 44. Under treatment for pernicious anaemia since Aug., 1940. Maintenance established on a dose of 2 c.cm. of liver extract parenterally every two months. In May, 1940, after her usual injection, she developed generalized urticaria and collapsed. On three more occasions she developed urticaria after her injection. In Jan., 1942, intradermal tests with 0.1 c.cm. of liver extract were strongly positive. This patient has been unable to spare the time for frequent attendances at the hospital, and in her case no serious attempt at desensitization has therefore been made. She attends every six weeks and receives her requirement of liver extract in divided doses, starting at 0.1 c.cm., with increments of 0.1 c.cm. at intervals of 20 minutes until the first signs of intolerance appear; these in this case are flushing of the face and a feeling of tightness of the throat, and usually appear after a single dose of 0.3 to 0.4 c.cm. She then goes home and returns on the following day, when we have found the injections to be well tolerated. Dosage is started at the level reached on the previous day and proceeds at increments of 0.2 c.cm. at 20-minute intervals. The full requirement of 4 c.cm. for six weeks is usually injected in two days.

In all our cases the symptoms of intolerance to liver injections appeared only after several months or years of parenteral treatment; the interval between the injections was at least six weeks, for the reason that no patients under maintenance treatment in this department receive their injections at shorter periods.

Discussion

In view of the facts there is every reason to suppose that the intolerance is an anaphylactoid phenomenon and due to "allergic" sensitization, the liver acting as an antigen. This is the usually accepted view (Criepe, 1938; Jones, 1939). Our experience, using different brands and types of liver extract, would lead us to believe that none are free from bodies capable of this antigenic action. Various methods of desensitization have been suggested: splenic extract (Schlesinger, 1930); histamine (Corelli, 1935); "quotentin," which appears to be an empirical remedy alleged to contain hypophysial, parathyroid,

and suprarenal extracts (Lasch, 1936); various preparations of calcium (Lasch, 1936; v. Herff, 1937; Gigante, 1939); liver powder orally in increasing dosage (Diena, 1938); and the parenteral injection of liver extract in divided and increasing dosage (Engel, 1933; Grün, 1933, 1934; Krantz, 1938). This last, in view of known facts as to sensitization and allergy, appears to be rational, and was therefore adopted in this investigation.

That negative skin tests do not exclude intolerance to liver extract is shown by Case 2, in which these were negative 18 months after the onset of symptoms and became positive only during the attempt at desensitization. Two methods may be adopted for the parenteral administration of liver extract to intolerant patients: lasting desensitization can be achieved by a course of liver injections in increasing doses over several weeks; alternatively, the required dose may be given in small injections, preferably over two days. The latter method does not increase the tolerance of the patient to future doses.

Summary

Three cases of pernicious anaemia are described in which the patient had become "sensitive" to the parenteral injection of liver extract.

Skin tests cannot be relied upon to indicate intolerance.

By the use of divided doses of liver extract over a period of several weeks it proved possible to desensitize two patients to the extent that they became able to tolerate their full requirement of liver extract in one injection at monthly intervals. In a third case the required dose is being given in small injections over two days without attempt at permanent desensitization.

My thanks are due to Dr. S. C. Dyke for access to records and advice, and to Sister Dora Martin for care and supervision of the patients while in the wards.

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Medical Memoranda

Irritation of the Urinary Tract by "Doped" Beer

On the afternoon of Oct. 6, 1942, two ratings reported sick on board, one with the clinical features of acute pyelitis and the other with those of acute anterior urethritis. Provisionally these were regarded as infections with *B. coli communis* and the gonococcus respectively, and in both cases treatment with sulphapyridine and alkalis was instituted. There appeared, however, to be something unusual about these cases. First, acute pyelitis is an uncommon condition in young men; and, secondly, the rating with urethritis had a temperature of 102° F., with only a very slight mucous discharge. This pointed to the possibility of some causative factor common to both, and on close questioning it transpired that these two men and a companion had on the previous afternoon visited a brothel when the ship had put into port for a few hours. There they had had some beer, which, though it tasted normal, probably contained an aphrodisiac of the nature of cantharides, which had acted as a violent irritant of the urinary tract. It is known that for business purposes the proprietors of brothels do "dope" their drinks in this way, and naval personnel are advised never to quench their thirst at such places.

The third rating in the party complained of no symptoms whatever, and subsequent microscopical examination of his urine revealed no evidence that he had been affected. The stories of all three, however, combined to make it clear that he had drunk much less beer than his two companions, and that the one with pyelitis had had considerably more than the one with urethritis. There was thus a fairly close correlation between the amount of suspected beer consumed and the severity of the subsequent symptoms.

CASE RECORDS

Case 1.—Able Seaman "X," aged 22, reported sick on Oct. 6, 1942, complaining of severe pain in the penis at the end of micturition during the past few hours; he was passing water about every half-

hour with some urgency. Aching pain was also felt across the loins, spreading down the back of the thighs into the calves. Frontal headache and nausea were present. He had never had a similar attack in the past nor any other urinary trouble. Examination showed: temperature 103° F.; tongue furred; tenderness in both loins and over the pubes; neither kidney palpable. The urine was cloudy, with a naked-eye deposit of pus on being left to stand. (Microscopy was not possible until two days later.) Progress was as follows: Oct. 7: Restless the previous night and vomited four times. Morning and evening temperatures 99.2° and 98.4° F. respectively. Frequency becoming less. Oct. 8: Pain now present during whole act of micturition. Nausea and generalized abdominal discomfort. Tender in both renal angles. B.P. 110/80. Urine clear to naked-eye inspection, but many pus cells and an occasional red cell seen on microscopy; no casts or organisms seen. Oct. 9: All symptoms diminished, but back still weak. Developing herpes labialis. Some pus cells and an occasional red cell present in urine. Oct. 14: Return of pain in the back and painful micturition. Temperature up to 101° F. Tender in loins, above Poupart's ligaments, and over pubes. Many more pus cells present in urine. Oct. 22: Patient completely recovered; symptomless; no pus cells visible even in a centrifuged specimen.

Case 2.—Able Seaman "Y," aged 24, reported sick on Oct. 6, 1942, complaining of pain in the penis on micturition during the past few hours; pain worse at the end of the act; a little frequency but no urgency. Intercourse the previous afternoon and five days before. No history of similar trouble or of venereal disease in the past. Examination revealed a temperature of 102° F. and very slight mucous discharge from urethra. (A smear taken before starting treatment with sulphapyridine was subsequently shown to contain a very few pus and epithelial cells only—no gonococci.) Progress was as follows: Oct. 7: Passed water four times the previous night; complaining of nausea and dizziness; temperature normal all day. Oct. 8: Appetite returning; pain during micturition still present; no urethral discharge. Many pus cells seen in urine on microscopy. Oct. 9: Urine contained a few pus cells. Oct. 11: Feeling well; symptomless; only a very occasional pus cell seen in urine.

COMMENT

One case each of acute pyelitis and acute anterior urethritis are described, both suspected of being due to an aphrodisiac taken in beer consumed at a brothel. Unfortunately there has so far been no opportunity for making further inquiries concerning the nature of the suspected "dope."

Between them these two cases present an interesting study of the symptoms produced by irritation of the urinary tract from renal pelvis to anterior urethra, and it is regretted that, owing to the difficulties of practising medicine on board a destroyer, it was not possible to investigate them in further detail.

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Influenzal Meningitis in a Child aged 2 treated with Sulphapyridine: Recovery

The following case is of interest as an example of the successful treatment of influenzal meningitis with sulphapyridine. A similar case has recently been reported by Birch in a child aged 3.

CASE HISTORY

The patient, a boy aged 2, was admitted to hospital on Dec. 11, 1942, with a week's history of a running nose and general malaise. Two days before admission he had a convulsion and became drowsy, and this was followed in a few hours by the onset of diarrhoea and vomiting, with constant twitching and rolling of the eyes. He had a past history of recurrent otitis media of the right ear, and measles five weeks before admission. He was the youngest of a family of four, the others being healthy.

When first seen he had a temperature of 100.4° and was drowsy and confused, with marked neck stiffness and a positive Kernig's sign. The right ear-drum was pink and opaque; the left one was normal. Lumbar puncture was performed, and the cerebrospinal fluid on the second day of illness was turbid and under increased pressure. It contained 2,740 cells per c.mm.—85% polymorphs—protein 190 mg. per 100 c.mm., and chlorides 755 mg. per 100 c.mm.; sugar was present. Sulphapyridine was started, with an initial dose of 1 g. followed by 0.5 g. four-hourly. The following day the child was still vomiting, and an intravenous infusion of 5% glucose in normal saline was given. He was very restless, and the temperature was still raised, but the right drum was no longer injected. The C.S.F. had grown a pure culture of a Gram-negative haemophilic organism, subsequently identified as *H. influenzae* on its requirement of both X and V factors. On the third day the child was very much improved; the temperature had fallen, and the saline infusion was stopped. Sulphapyridine was given in a reduced dose for a further five days, making eight days in all and a total of 17 g. On the tenth day the C.S.F. was sterile, and contained only 35 cells per c.mm., of which 80% were lymphocytes.

The temperature continued to fluctuate between 97° and 100° for three weeks, but the child was apparently well and had no physical signs. He was discharged on January 15, 1943, when he had been afebrile for a fortnight.

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